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HEALTH TECHNOLOGY BRIEFING
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Lumasiran for primary hyperoxaluria type 1 in paediatric patients aged up to 5 years

NIHRIO ID	27163	**NICE ID**	10233
Developer/Company	Alnylam Pharmaceuticals Inc.	**UKPS ID**	651681

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Lumasiran is in clinical development for the treatment of primary hyperoxaluria type I (PH1) in paediatric patients up to 5 years old. PH1 is a very rare disease caused by certain genetic mutations, in which excess production of a substance called oxalate results in the deposition of oxalate crystals in the kidneys and urinary tract. This leads to stone formation and kidney failure with significant morbidity and mortality. Treatment options for PH1 include vitamin B6 which is known to reduce the body's production of oxalate, dietary recommendations to prevent kidney stones and combined liver-kidney transplantation before or after development of end-stage kidney failure.

Lumasiran, which is administered as a subcutaneous injection, is designed to reduce the levels of an enzyme called glycolate oxidase produced by the liver. Oxalate production is therefore inhibited. By reducing oxalate production, lumasiran has the potential to prevent the actual disease process that develops in PH1. If licensed, lumasiran may provide the first pharmacological treatment option for paediatric patients with PH1 who do not have any approved treatment.

PROPOSED INDICATION

Treatment of primary hyperoxaluria type I (PH1) in children up to 5 years of age.[1]

TECHNOLOGY

DESCRIPTION

Lumasiran (ALN-GO1) is an investigational RNA interference (RNAi) therapeutic agent which utilises the natural cellular process of gene silencing to target glycolate oxidase (GO).[2] Suppression of GO activity should inhibit oxalate production while causing an accumulation of glycolate, which is soluble and thus readily excreted in the urine.[3] By reducing hepatic levels of the GO enzyme, and depleting the substrate necessary for oxalate production, lumasiran has the potential to potentially prevent the pathology that develops in PH1.[3-5]

Lumasiran is in clinical development for the treatment of PH1. In the phase III clinical trial programme (ILLUMINATE-B; NCT03905694), patients receive lumasiran by subcutaneous injection at a dose and schedule determined by body weight.[a] The lumasiran dose for patients with body weight ≥ 20kg is 3.0 mg/kg monthly x 3 doses (loading dose) followed by 3.0 mg/kg every-3-months (maintenance dose). For children weighing ⩾10 to 20 kg, the regimen is 6.0 mg/kg monthly x 3 doses (loading dose) followed by 6.0 mg/kg every-3-months (maintenance dose). For children weighing less than 10 kg, the regimen is 6.0 mg/kg monthly x 3 doses (loading dose) followed by 3.0 mg/kg monthly (maintenance dose).[b]

INNOVATION AND/OR ADVANTAGES

Currently, no approved therapeutics exist for the treatment of PH1. Whilst vitamin B6 works for a subset of patients, the only effective treatment is a combined liver-kidney transplant that is associated with significant morbidity and mortality. Therefore, there is a significant unmet need for an efficacious and robust treatment to stop liver oxalate production and prevent disease progression without the need for liver transplant in patients with PH1.[3]

Lumasiran utilizes Alnylam's Enhanced Stabilization Chemistry (ESC)-GalNAc conjugate technology, which enables subcutaneous dosing with increased potency and durability and a wide therapeutic index.[2] Specifically, the use of the ESC technology demonstrated a 5- to 10-fold higher potency for ESC siRNAs versus the earlier standard template chemistry (STC) siRNAs in vivo.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Lumasiran does not currently have a Marketing Authorisation in the EU/UK for any indication.

Lumasiran has the following regulatory designations/awards:
an orphan designation in the EU awarded in March 2016 for primary hyperoxaluria[7]

- a PRIME scheme eligibility was granted by the EMA in March 2018 for PH1[8]

[a] Information provided by Alnylam Pharmaceuticals.
[b] Information provided by Alnylam Pharmaceuticals.

PATIENT GROUP

DISEASE BACKGROUND

Primary hyperoxaluria (PH) is an ultra-orphan disease caused by genetic mutations, which results in the build-up of overproduction and accumulation of oxalate in the body. This results in the deposition of calcium oxalate crystals in the kidneys and urinary tract, resulting in urolithiasis, nephrocalcinosis, and ultimately kidney failure.[9,10] As a result of systemic oxalosis, multi-organ damage occurs which affects bones, eyes, skin and the heart.[10]

There are three main types of PH that are inherited in an autosomal recessive pattern: PH1, PH2 and PH3. PH1 is caused by a deficiency of the liver specific, peroxisomal enzyme alanine/glyoxylate aminotransferase (AGT), and is the most severe primary hyperoxaluria[11] and accounts for approximately 80% of cases.[9,11,12] Approximately 50% of patients will have kidney failure by age 15 years, and about 80% will have end-stage renal disease by age 30 years.[10]

Signs and symptoms of PH1 vary in severity and may begin any time from infancy to early adulthood.[13]

CLINICAL NEED AND BURDEN OF DISEASE

PH1 has an estimated prevalence of 1 to 3 cases per 1 million population and an incidence rate of approximately 120,000 live births per year in Europe.[9] It accounts for 1-2% of paediatric end-stage kidney disease but higher values are reported in specific populations with a high rate of consanguinity.[9,14]

The UK-based National Renal Rare Disease Registry (RaDaR) suggests there were 96 patients across English and Scottish hospitals who have hyperoxaluria as of 2018.[15] Assuming 80% of cases of PH are PH1,[12] there are approximately 77 patients in England and Scotland who suffer from PH1.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment for PH1 centres on minimising calcium oxalate deposition and the maintenance of renal function. A number of treatment options for preventing kidney stones benefit all patients with PH1, these include:[13]

- Drinking large amount of fluid
- Oral potassium citrate to inhibit calcium in the urine
- Drugs such as thiazides to decrease calcium in the urine
- Avoiding significant intake of vitamin C or D (they promote stone formation)
- Supplementation of dietary calcium

Treatment for kidney stones may involve shock wave lithotripsy, percutaneous nephrolithotomy, and/or ureteroscopy.[13]

Combined liver-kidney transplantation is an option whether pre-emptive or after development of end-stage kidney damage.[16,17] Depending on response to other treatments and the disease severity, options may include combined liver-kidney transplant; sequential liver-kidney transplant; an isolated kidney transplant, or an isolated liver transplant. Transplantation requires life-long immune suppression and carries significant mortality risk.[13,18]

CURRENT TREATMENT OPTIONS

Currently, the only therapeutic technology known to reduce the body's production of oxalate is pyridoxine (vitamin B6), although other dietary recommendations have been advocated to prevent kidney stones. Although only 10-30% of people with PH1 respond to the treatment, it has been recommended all recently diagnosed people have a three-month trial.[13]

PLACE OF TECHNOLOGY

If licensed, lumasiran may provide the first pharmacological treatment option for patients aged up to 5 years with PH1, who do not currently have any approved treatment.

CLINICAL TRIAL INFORMATION

Trial	**ILLUMINATE-B, NCT03905694, EudraCT-2018-004014-17; children up to 5 yrs; lumasiran; phase III**
Sponsor	Alnylam Pharmaceuticals
Status	Recruiting
Source of Information	Trial registry[1,19]
Location	EU (incl UK), USA and Israel
Design	Single group assignment (open label)
Participants	n=20 (planned); aged up to 5 yrs; confirmation of PH1 disease; meets urinary oxalate excretion requirements; if taking vitamin B6, must have been on stable regimen for at least 90 days
Schedule	Subjects receive a multiple dose of lumasiran by subcutaneous injection. The lumasiran dose for patients weighing ⩾10 to 20 kg is 6.0 mg/kg monthly x 3 doses (loading dose) followed by 6.0 mg/kg every-3-months (maintenance dose). For children weighing less than 10 kg, the regimen is 6.0 mg/kg monthly x 3 doses (loading dose) followed by 3.0 mg/kg monthly (maintenance dose).[c]
Follow-up	Patients will return to the clinical centre for follow-up assessment of efficacy, safety, tolerability, PK, PD, and patient and caregiver experience and burden until the last study visit. The estimated total time on study, inclusive of screening, for each patient is up to 62 months, including up to 2 months of screening followed by up to 60 months of treatment.[d]
Primary Outcomes[1]	Percentage change in urinary oxalate excretion from baseline to mth 6 [Time frame: up to 6 mths]
Secondary Outcomes[1]	• Percentage change in urinary oxalate excretion from baseline to end of study (mth 60) [Time frame: up to 60 mths] • Absolute change in urinary oxalate excretion from baseline [Time frame: up to 60 mths] • Percentage of participants with urinary oxalate excretion ≤ the upper limit of normal (ULN) and ≤ 1.5 x ULN [Time frame: up to 60 mths] • Maximum observed plasma concentration (Cmax) of lumasiran [Time frame: up to 24 mths] • Time to maximum observed plasma concentration (tmax) of lumasiran [Time frame: up to 24 mths] • Elimination half-life (t1/2beta) of lumasiran [Time frame: up to 24 mths]

[c] Information provided by Alnylam Pharmaceuticals
[d] Information provided by Alnylam Pharmaceuticals.

	• Area under the concentration-time curve (AUC) of lumasiran [Time frame: up to 24 mths] • Apparent clearance (CL/F) of lumasiran [Time frame: up to 24 mths] • Apparent volume of distribution (V/F) of lumasiran [Time frame: up to 24 mths] • Change in estimated glomerular filtration rate (eGFR) from baseline [Time frame: up to 60 mths] • Frequency of adverse events (AEs) [Time frame: up to 60 mths]
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Estimated primary completion date March 2020. Estimated study completion date February 2024.

ESTIMATED COST

The cost of lumasiran is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Adult). E06/S/a.
- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Children). E06/S/b.

OTHER GUIDANCE

No relevant guidance identified.

ADDITIONAL INFORMATION

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